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CASE REPORT

Clinical and histologic outcome in a dog surviving massive hepatic necrosis

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This report describes the clinical and histologic recovery of a 2-year-old mixed-breed dog presented with hypovolemic shock, markedly increased serum alanine amino transferase activity, and hemoabdomen. Emergency exploratory surgery revealed a friable liver with multiple capsule hemorrhages necessitating removal of the left lateral lobe. Histologic evaluation showed acute massive hepatic necrosis with centrilobular and midzonal distribution. The dog survived, and all monitored laboratory values normalized within 7 weeks. A liver biopsy taken 8 weeks after presentation revealed normal hepatic architecture with a few, randomly distributed neutrophilic foci. Follow-up included intermittent determination of liver variables including liver function tests for a period of 7 years. The dog's health status, and all test results remained normal during this time. Complete recovery and good long-term quality of life after life-threatening acute liver failure secondary to massive hepatic necrosis is possible in dogs.

KEYWORDS

acute, canine, hemoabdomen, histology, liver failure, shock

1 | CASE REPORT

A 2-year-old mixed-breed dog (male, neutered) weighing 10.8 kg (23.8 lb) with a body condition score (BCS) of 5 out of 9 was admitted to our clinic with a history of acute weakness and 1 episode of vomiting. Approximately 8 hours before admission, the owner had returned from a hike in the Alps where the dog was off-leash and was seen playing briefly with mushrooms, although ingestion was not observed. Physical examination showed hypothermia (rectal temperature, 35.1°C [95°F]), pale mucous membranes, a prolonged capillary refill time of 3 seconds, weak femoral pulses, tachycardia, tachypnea, and a painful abdomen. Systolic blood pressure was immeasurably low. Laboratory analyses showed normochromic, normocytic anemia (hematocrit 30%; reference range [RR] 42%-55%), hypoproteinemia (32 g/L, RR 55-71 g/L), hypoalbuminemia (17 g/L, RR 29-37 g/L), serum alanine amino transferase activity (ALT) activity greater than the upper limit of detection (>6000 U/L, RR 20-93 U/L), and hyperlactacidemia (8.2 mmol/L, RR 0-2 mmol/L). Thoracic radiographs

showed a small cardiac silhouette and vena cava. Abdominal radiographs showed loss of serosal detail and liver with normal size and shape. Abdominal ultrasonography showed moderate amounts of free abdominal fluid and a moderately hyperechoic liver parenchyma. An activated clotting time (Hemochron 401 Analyzer; Soma Technology, Inc, Bloomfield, CT) was prolonged at 223 seconds (RR, 60-125 seconds) with normal platelet count (236 000 platelets/ μ L, RR 130 000-400 000/ μ L). The results of abdominal fluid analysis (hematocrit 37%, total protein 38 g/L) were compatible with acute hemoabdomen. Volume replacement treatment with isotonic-lactated Ringer's solution and colloids (6% hetastarch solution) was continuously adjusted based on vital signs and blood pressure measurements. After the 1st fluid resuscitation, the mean arterial pressure had increased to 65 mm Hg and remained between approximately 60 and 70 mm Hg for the 1st 24 hours. The goal was to avoid overly aggressive fluid administration as this was believed to further exacerbate hemorrhage. Esomeprazole (1 mg/kg IV q12h; Esomep IV, Astra Zeneca, Zug, Switzerland), ondasetron (0.2 mg/kg IV q12h; Labatec Pharma, Meyrin, Switzerland), and vitamin K (2 mg/kg IV q12h; Konaktion MM, Roche Pharma, Switzerland) were also administered. After 24 hours of treatment, the dog had a hematocrit of 12%,

Abbreviations: ALF, acute liver failure; ALT, alanine amino transferase activity; aPTT, activated partial thromboplastin time; BCS, body condition score; HPC, hepatic progenitor cells; PT, prothrombin time; RR, reference range.

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a refractometric total plasma protein concentration of 16 g/L, and a platelet count of 51 000/ μ L. At this time, serum bilirubin concentration (11.7 μ mol/L; RR 0-3.5 μ mol/L) and alkaline phosphatase (ALP) activity (87 U/L; RR 20-98 U/L) were also measured. Alanine amino transferase activity was 6799 U/L (RR 20-93 U/L). Administration of 200 mL fresh frozen plasma and 150 mL packed red blood cells led to increases in the hematocrit (25%) and total plasma protein concentration (32 g/L). Capillary blood glucose was continuously assessed and remained within the RR (4-6 mmol/L). After 36 hours of treatment, the hematocrit and total plasma protein concentration had again decreased to 12% and 20 g/L, respectively, and an exploratory celiotomy was elected. Coagulation status was reevaluated and showed a prolonged prothrombin time (PT) at 25.6 seconds (RR, 6.3-8.5 seconds) and activated partial thromboplastin time (aPTT) at 24.1 seconds (RR, 9.6-16.1 seconds), and the platelet count remained low at 29000/ μ L. A 2nd transfusion of fresh frozen plasma (200 mL) was administered. Intraoperatively, the liver was pale and friable with multiple small elongated hemorrhaging serosal fissures on all liver lobes. A larger, approximately 6 mm, oozing hepatic capsular rupture on the left lateral lobe was observed to increase in size with minimal pressure. Therefore, the left lateral lobe was removed using a stapling device, and no further hemorrhage was seen. No other liver biopsies were taken. Postoperatively, the dog developed generalized peripheral edema, and therefore, 1 transfusion with human albumin (2 g/kg over 5 hours; Albumin CSL 20%, CSL Behring AG, Bern, Switzerland) was administered. Twenty-four hours after surgery, gradual clinical improvement was noted, and the dog started to eat small amount of a highly digestible diet when hand-fed. Serum bilirubin concentration and ALP activity had risen to 37.7 μ mol/L (RR, 0-3.5 μ mol/L) and 183 U/L (RR, 20-98 U/L), whereas ALT activity had decreased to 2365 U/L (RR, 20-93 U/L) (Supporting Information Table 2). Supportive treatment in addition to fluid therapy, ondansetron, and esomeprazole consisted of amoxicillin (20 mg/kg IV q8h; Clamoxyl 1 g, GlaxoSmithKline, Switzerland), S-adenosylmethionine (450 mg PO q24 h; Denosyl 225 mg, Nutramax, Edgewood, MD), and ursodeoxycholic acid (15 mg/kg PO q24h; De-Ursil, CPS Cito Pharma, Uster, Switzerland).

Histologic examination showed a zonal distribution pattern of massive coagulative necrosis that affected all liver lobules. The necrosis extended from the centrilobular regions over the midzonal area to the portal fields, sparing only a small rim of hepatocytes around the portal triad and limiting plate (Figures 1 and 2). Necrotic hepatocytes were characterized by hyperesinophilic cytoplasm and loss of nuclei. Necrotic areas were sharply demarcated from the remaining viable tissue. In the adjacent parenchyma, sinusoids appeared markedly congested with multifocal leukocytostasis without neutrophilic infiltration of the parenchyma. The diagnosis was massive acute hepatic necrosis.

The dog continued to improve clinically and was discharged on day 6 after surgery. By the time of discharge, the hematocrit had increased to 24% with an adequate regenerative response, serum protein concentration was nearly normal, and ALT activity had decreased to 1917 U/L (Supporting Information Tables 1 and 2). The owner was advised to continue administering amoxicillin and omeprazole for 1 week and S-adenosylmethionine and ursodeoxycholic acid for another 6 weeks.

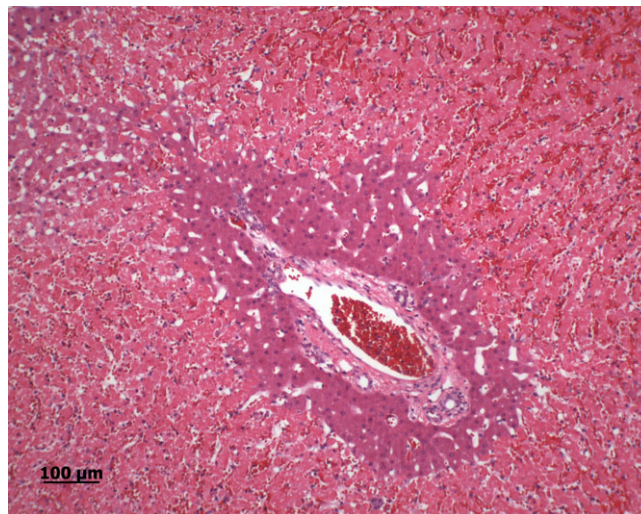


FIGURE 1 Liver, ruptured left lateral lobe. Hematoxylin and eosin staining: Acute panlobular necrosis with surviving periportal hepatocytes. The necrosis is sharply demarcated, and the sinusoids are congested

At the 1st reexamination 1 week after discharge, clinical abnormalities included a higher sleep requirement than normal and pale pink mucous membranes. The hematocrit had increased to 34%, ALT activity had substantially decreased to 308 U/L, serum bilirubin concentration had decreased to 4.5 μ mol/L (0-3.5 μ mol/L), and ALP activity had normalized (Supporting Information Table 3). The dog was clinically normal at the 2nd reexamination 3 weeks after discharge, and the only laboratory abnormality was mild anemia (Supporting Information Table 3). The results of all laboratory tests were normal at the 3rd reexamination 7 weeks after discharge. Ultrasonography of the liver showed mildly heterogeneous parenchymal echogenicity. At this point, the benefit of follow-up histologic examination of the liver to assess hepatic regeneration (*restitutio ad integrum* versus progression to chronic changes)¹ was discussed, and collection of liver biopsy specimens was planned for the next day. Coagulation times (PT, aPTT)

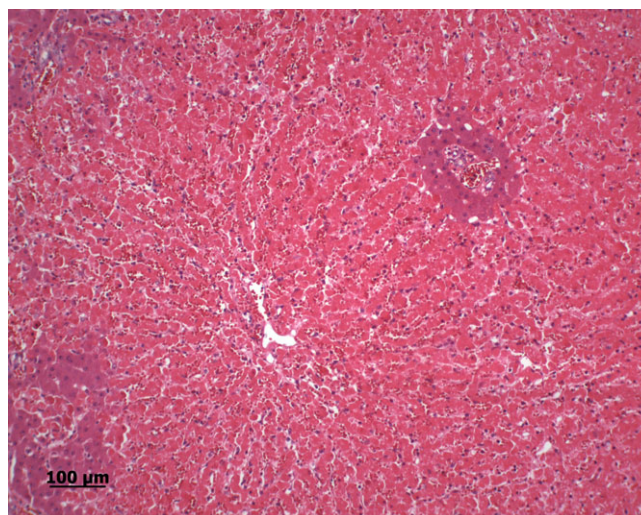


FIGURE 2 Liver, ruptured left lateral lobe. Hematoxylin and eosin staining: Acute panlobular necrosis with surviving periportal hepatocytes between 2 portal fields

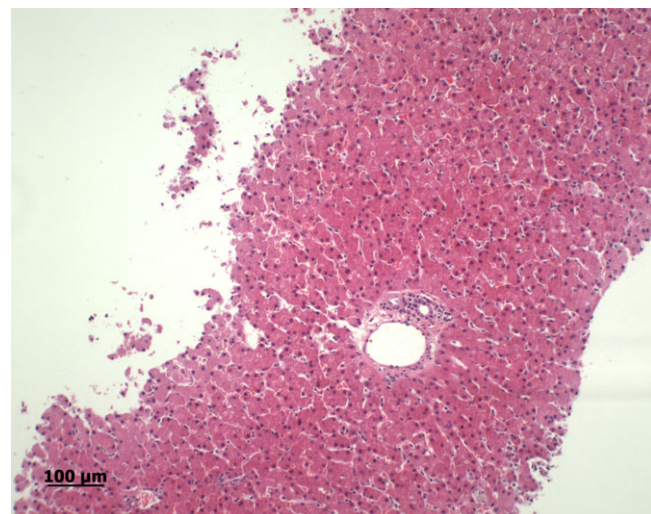


FIGURE 3 Tru-Cut biopsy taken 8 weeks after initial presentation. Hematoxylin and eosin staining: Normal liver architecture, hepatocytes show normal morphology, the portal field contains an unaltered bile duct, normally sized portal vein, and normal artery. There is minimal periportal neutrophilic infiltration

were normal, and 2 ultrasound-guided percutaneous Tru-Cut liver biopsy specimens (16 gauge needle) were obtained under brief propofol anesthesia from the right lateral lobe.

Histologically, the hepatic architecture was regularly distributed, and the distance from the central vein to the portal field was normal. The hepatocytes appeared normal in size and morphology with no increase in intracytoplasmic pigments. The spaces of Disse and the bile canaliculi were not visible with hematoxylin and eosin stain (Figure 3). Multifocal aggregates of macrophages with yellowish brown intracytoplasmic pigment (lipofuscin) (Figure 4) were seen in small numbers within the parenchyma. Isolated neutrophils were seen at the interface of the limiting plate and portal tracts (Figure 4). There

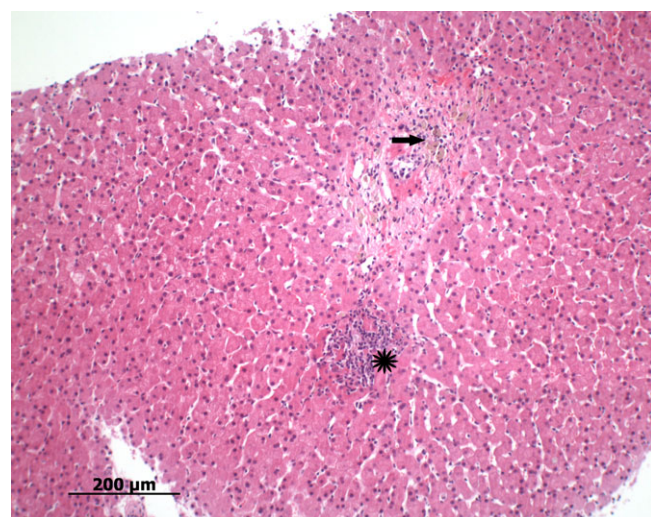


FIGURE 4 Tru-Cut biopsy taken 8 weeks after initial presentation. Hematoxylin and eosin staining: Minimal periportal inflammation consisting of neutrophils, small clusters of macrophages with intracytoplasmic yellow to gold brown pigment (lipofuscin, arrow), and residual degeneration. In the adjacent liver parenchyma at the limiting plate small cluster of neutrophils (asterisk)

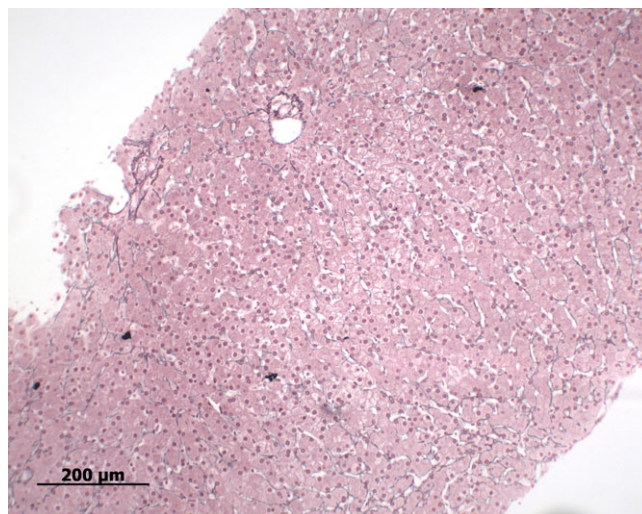


FIGURE 5 Tru-Cut biopsy taken 8 weeks after initial presentation. Reticulin staining: Reticulin fibers represented by a fine network of fibers between hepatocytes. The amount of reticulin fibers around portal fields, central vein, and in the midzone of hepatic lobules was deemed normal

was no evidence of scar tissue, regenerative nodules, or noticeable progression toward chronic hepatitis. Even distribution of a very fine network of reticulin fibers between the hepatocytes was seen in all hepatic lobules (Figure 5). This network was interpreted as normal. The mild neutrophilic infiltration and aggregates of macrophages with intracytoplasmic lipofuscin were interpreted as a remnant reparative process after acute liver injury.

Follow-up telephone calls for the next several years indicated that the dog was normal and active. A general health checkup 5 years after initial treatment showed no abnormalities on physical examination with a BCS of 5 out of 9 (11.8 kg, [26 lb]). Results of a CBC, serum biochemistry panel, and urinalysis were all normal (Supporting Information Table 3). Liver function testing consisting of preprandial and postprandial serum bile acid concentration as well as plasma ammonium concentration was normal. The radiographic liver size based on gastric axis position was slightly smaller than normal; however, it was unclear whether this was because of lobectomy or fibrosis. Hepatic ultrasonography was not done because of its low sensitivity and specificity for detection of parenchymal abnormalities.^{2,3} At the time of manuscript preparation (7 years after initial presentation), the dog is still in excellent health. Results of routine predental laboratory testing (CBC, serum biochemistry panel) were all normal (Supporting Information Table 3).

2 | DISCUSSION

This case report is noteworthy because it provides veterinarians with information on the histologic and clinical long-term recovery of a dog with acute liver failure (ALF) caused by massive hepatic necrosis. Information such as this is invaluable for providing owners with the possibility for a positive long-term outcome.

In dogs, ALF is defined as the development of acute clinical signs with concurrent hyperbilirubinemia and coagulopathy.⁴ Because of

the fulminant course of the disease, ALF is mainly a clinical diagnosis because obtaining hepatic biopsy specimens is considered a life-threatening procedure. In the present case, uncontrollable hepatic hemorrhage necessitating emergency exploratory surgery enabled collection of liver specimen for histologic examination. In retrospect, this surgical intervention appears curative, but at the time, we considered it a last resort and the owner was given a grave prognosis. It proved challenging when discussing the prognosis with the owner because of the lack of information available for estimating possible survival and long-term outcomes in dogs with ALF.

Different patterns of hepatocellular necrosis can be distinguished histologically and comprise focal or multifocal, randomly distributed necrosis, piecemeal necrosis, zonal necrosis, and lobular necrosis.⁵ Lobular necrosis can further be subdivided into centrilobular, periportal, and panlobular (massive) necrosis.⁵ Focal or multifocal necrosis with a random distribution occurs in hematogenous infections, and centrilobular necrosis is a common sequela of intoxications^{6–9} and hypoxia;⁵ however, it occurs in certain viral infections (adenovirus 1) of dogs.¹⁰ Some intoxications can cause only midzonal necrosis or periportal necrosis; however, this is rather uncommon.⁵

Acute liver failure in dogs has been associated with toxins and toxicants,^{6–9,11} drugs,^{12–15} neoplasia,⁴ and infection.^{7,16} In a recent study of 49 dogs with ALF, the cause was identified in roughly one third and comprised neoplasia, presumptive leptospirosis, and ischemia.⁴ The remaining two thirds were deemed idiopathic although exposure to hepatotoxins and toxicants was frequently suspected.⁴ In the present case, exposure to hepatotoxic mushrooms (*Amanita* spp.) was suspected but could not be verified. Although histologic lesions are not specific or pathognomonic for a single toxin/toxicant, the histologic findings in our case were similar to lesions described in proven amanitin toxicosis in dogs⁷ and cats.⁵ Clinical signs of amanitin toxicosis, consisting of fulminant multi-organ failure including liver and less commonly kidneys, become apparent approximately 36–84 hours after exposure to amanitins.¹⁷ The time course and severity of clinical signs depend on the ingested dose, and death can ensue within 24 hours of ingesting large doses of amanitins in dogs.¹⁸ Although select veterinary toxicology laboratories provide amanitin testing, there is unfortunately no retrospective method to detect amanitin toxin, and a definitive diagnosis requires examining fresh liver tissue or urine specimens.⁹

A vascular incident leading to ischemic necrosis was also initially considered. However, evidence of vascular infarction or thromboembolism was not found at surgery, and diseases known to predispose to thromboembolism were not identified.

To our knowledge, there is no information on the results of follow-up assessment of dogs that survive ALF caused by massive liver necrosis. In the largest study on canine ALF, 7 of the 49 (14.3%) dogs survived to the time of discharge, but no follow-up data were given.⁴ Follow-up information was also not provided in a recent study describing dogs with food-borne hepatic aflatoxicosis.¹¹ There are 2 reports that include follow-up information on dogs that survived ALF based on clinical results.^{8,9} One of the cases was a dog with ALF caused by ingestion of blue-green algae (*Microcystis* spp.), and follow-up information was limited to 12 days.⁹ The 2nd case report on a dog

with ALF because of xylitol ingestion included clinical and clinicopathologic information for 7 months after the initial toxicosis.⁸

Histologic reassessment of liver biopsy specimens in the present case showed complete restoration of the hepatic architecture. Although a plethora of experimental data on hepatic regeneration in dogs exists in the literature¹⁹ that might also be extrapolated to regenerative responses after massive necrosis, to our knowledge, there is no information regarding hepatic regeneration after acute hepatic necrosis in dogs. Available information focuses on carbon-tetrachloride-induced hepatic necrosis (administered over the course of 14–20 days),²⁰ and results suggest that histologic evidence of moderate necrosis and destruction of normal lobular architecture is still present 8 weeks after induction of necrosis.²⁰

Based on observations of young people with ALF, it has been proposed that a high proportion of surviving hepatocytes within necrotic parenchyma is not a prerequisite for native liver regeneration.²¹ In cases of complete hepatocyte regeneration, necrosis of up to 80% of the liver cell mass in resected native liver has been described.²¹ In the course of hepatocyte regeneration after massive hepatic necrosis, ductular cell proliferation plays an important role. These so-called “ductular reactions” composed of hepatic progenitor cells (HPC) probably emanate from the canals of Hering, located close to the limiting plate.²² In human hepatology, massive hepatocyte loss caused by viral infections or ingestion of toxic substances triggers an HPC response within 24 hours and a prominent ductular reaction can be observed. Proliferation is followed by differentiation, during which the ductular reactions give rise to “hepatocyte-like cells” also identified as intermediate hepatocytes.²³ In dogs, the involvement of the HPC compartment has also been described in acute hepatitis.²³ A ductular reaction has been observed localized to the site of injury, accompanied by intermediate cells.²⁴ Later, these cells then decrease in number and subsequently complete differentiation into hepatocytes.²⁵ In humans, sequential histologic evaluation after massive hepatic necrosis because of fulminant viral hepatitis B infection showed that liver cell regeneration started with proliferation of HPC at 7–10 days after auxiliary partial orthotopic liver transplantation.²⁶ Hepatocyte differentiation of HPC occurred close to 1 month after transplantation. At 2 months, there was no evidence of necrosis, ductules decreased in number, and numerous individual hepatocytes appeared in the native liver.²⁶

The hepatic regenerative process in our case appeared rapid and extensive. At 8 weeks, there was no histologic evidence of embryonic ductule buds, and only fully developed hepatocytes, lobules, and portal triads were seen. We also found it remarkable that such marked panlobular necrosis was followed by complete regeneration without evidence of fibrotic changes. The scattered foci of neutrophilic infiltration were believed to reflect a remnant reparative response. Concurrent normalization of liver enzyme activities and indirect liver function variables further supported the theory of a rapid healing response. The 2nd histologic evaluation did not strictly reflect the regenerative response to the initial insult of necrosis because the most severely affected hemorrhaging lobe had been removed. A limitation of this case report is the lack of biopsies from additional liver lobes; however, it was assumed that the disease process was affecting the entire liver based on the gross appearance during surgery.

In addition to factors such as the etiology of the disease and results of clinical and laboratory testing, the time chosen for re-biopsy of the liver is likely crucial for detecting the development of chronic changes. Our decision was based on work by Poldervaart et al who reported that a fraction (5/12 repeatedly sampled dogs) of dogs with acute hepatitis went on to develop chronic hepatic disease.¹ The authors suggested that early recognition and treatment with corticosteroids are of key importance for prevention of disease progression and increased survival time. It is difficult to compare our case to results of that study as details on the severity of necroinflammatory lesions in the repeatedly sampled dogs with "acute hepatitis" were not provided. In that study, dogs with "severe acute hepatitis" died, and the remaining acute hepatitis cases that underwent a 2nd liver biopsy 6 weeks later very likely represented disease entities that differed from our case.¹ We ultimately decided to refrain from treatment with corticosteroids because the amount of reticulin fibers was deemed normal. In addition, the owner did not want to pursue collection of further liver biopsy specimens for assessment of the degree of hepatic fibrosis.

In summary, this case report describes complete and long-term recovery from life-threatening ALF caused by massive hepatic necrosis in a dog. Potential later subclinical chronic hepatic remodeling did not affect quality of life and was not evident based on the results of routine liver function testing. Even if the etiology remains unknown and the presented outcome might not be transferrable to other types of hepatic necrosis or ALF, this case report serves as a valuable reference for veterinarians who need information to base their decisions when dealing with similar cases. It is important to recognize that long-term survival with adequate hepatic regeneration and a good quality of life is possible even in severe cases of ALF.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

The authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

The authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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